3. The non-technical abstract

People with diabetes commonly develop temporary or permanent damage to nerve tissue. Nerve injuries are caused by decreased blood flow and high blood sugar levels and are more likely to develop if blood-glucose levels are poorly controlled. Nerve damage may affect peripheral nerves in the arms and/or the legs. Nerve injury or neuropathy may begin with intermittent pain and tingling in the extremities, particularly the feet. In later stages, the pain is more intense and constant. Finally, a painless neuropathy develops when pain sensation is lost to an area. This greatly increases the risk of severe tissue injury because pain can no longer alert the person to injury. Currently there are no therapies available to treat this condition. The purpose of this clinical study is to assess the effect of gene therapy delivered near the large peripheral nerves in the leg in patients with advanced diabetic neuropathy.

Animal studies were performed to see how vascular endothelial growth factor (VEGF) DNA would affect the blood supply around the large nerves in the legs as well as the nerves themselves. From these studies, it appears that the blood supply to the nerves and the nerve fibers were restored after treatment with the VEGF gene. In addition, during a clinical trial with this same gene in patients with poor circulation in their legs, there were several patients treated who happened to also have diabetic neuropathy. These patients observed that they could feel sensation in their previously numb foot or leg after receiving VEGF gene. These observations along with the previous studies suggested the need to test VEGF gene in diabetic neuropathy patients in a controlled clinical trial. The study objectives are to look at the safety and possibly effect of VEGF gene transfer in patients with diabetic neuropathy. There are two groups of patients to be studied, one group has poor circulation in their legs and neuropathy while the second group has normal circulation in their legs with their neuropathy. A total of 192 patients will be enrolled, 96 patients in each group (with and without poor leg circulation). Patients must be > 21 years old with diabetic neuropathy. All patients will be followed for 12 months and afterward will receive questionnaires to check on their well-being for another 14 years. There are three doses of the VEGF gene that will be tested. Patients will be enrolled in one of the three dose groups and be randomized to receive either VEGF gene or placebo (salt water). Patients will receive 8 intramuscular injections from the hip to the ankle of the leg to be treated. The injections will be repeated at 2 and 4 weeks. The patients will be followed and undergo testing of the nerve function in their legs to compare the initial condition to the possible effect of the gene therapy.